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Application of on-line Raman spectroscopy for characterizing relationships between drug hydration state and tablet physical stability

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Abstract

Experiments were conducted to elucidate the relationship between risedronate sodium (RS) hydration state and the physical stability of tablets containing RS. The RS crystal lattice contains channels occupied by water, which is removed by drying processes at temperatures below the boiling point of water, causing a reversible contraction of the crystal lattice. In this study, risedronate sodium was wet granulated followed by fluid bed drying to final granulation moisture contents between 1 and 7%, and then compressed into tablets. During drying, the RS solid-state form was continuously monitored using on-line Raman spectroscopy. Raman spectra acquired in these experiments enabled direct monitoring of changes in the RS crystal lattice, due to dehydration, which provided key information relating RS solid-state form characteristics to final granulation moisture content. Final granulation moisture was found to have a significant effect on the change in RS hydration state measured by Raman spectroscopy. As the final granulation moisture decreased, the amount of RS dehydrated form increased. The largest Raman spectral changes were in the C–H stretching region and the region including the 3-picoline ring and PO_2^- stretches. These changes are indicative of substantial changes in the RS solid-state structure. Final granulation moisture also had a significant effect on the change in tablet thickness over time. Lower final granulation moisture caused a greater increase in tablet thickness as the RS rehydrated. In addition, the change in RS hydration state during fluid bed drying, measured by on-line Raman, was correlated to the increase in tablet thickness and subsequent loss of tablet integrity. Raman spectroscopy allowed direct RS hydration state monitoring, rather than inference from a bulk moisture measurement. Development of a Process Analytical Technology (PAT), specifically Raman, to monitor RS solid-state during drying enabled establishment of relationships between fundamental hydration dynamics associated with RS and final product performance attributes.

Keywords: Raman; On-line spectroscopy; Hydration state; Physical stability; Fluid bed drying

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1. Introduction

Every pharmaceutical process has one or more mechanisms to control product quality. Historically, these mechanisms have been associated with the process. In order to relate them to product quality, inferences are made based on developed cause/effect relationships and/or physical chemical relationships. An example is control of wet granulation particle size by setting mixing speed, mixing time, granulating fluid flow rate, and total amount of granulating fluid. While these approaches can provide a repeatable process and high likelihood of a consistent product, they can become problematic if the process and formulation is not robust. For example, the process and formulation may not compensate for changes in raw material properties. Often minimal knowledge is acquired on the effect of batch to batch variation prior to marketing a drug product. When the product controls are process-related, a significant amount of time and money can be spent troubleshooting a process when the impact of variation is experienced over time. In addition, final product quality is traditionally determined at the end of the process. There is a delay of days to weeks between manufacture of the product and release testing. By the time a problem is discovered, multiple batches can be affected. Methodology, which directly measures an aspect of interest and quickly provides feedback on the quality of product, or could control the quality of product, can save time and money, and ensure the final product quality. The analytical methodology being exploited to this end has been called Process Analytical Technology (PAT). These analytical tools have more informing power than the process controls that are widely used, such as temperature, flow rate, and time.

A number of different technologies have been utilized to develop relationships between the physical chemical properties of drug product actives, excipients, or intermediates and final product performance. The most widely used on-line and at-line tool is near infrared reflectance (NIR) spectroscopy. Overtones and combinations of the fundamental mid-IR bending and stretching modes are detected in the near infrared region. Absorbances observed by NIR result mainly from the C–H, O–H, and N–H functional groups. NIR has several characteristics, which enable its use for diverse applications. NIR has a fast response time, requires no sample preparation, and is non-destructive. NIR testing has been used for the analysis of raw materials (Ciurczak, 1991), blending studies (Wargo and Drennen, 1996), assay (Ciurczak and Maldacker, 1986), determination of polymorphs (DeBraekeleer et al., 1998), particle size (O'Neil et al., 1999), moisture (Derksen et al., 1998; Kamet et al., 1989), and tablet hardness (Kirsch and Drennen, 1999). NIR is intrinsically well-suited to measuring the amount of water in a sample, because the greatest extinction coefficient in NIR is provided by water (Burns and Ciurczak, 2001). It has been utilized to decrease cycle time of fluid bed drying (Wildfong et al., 2002; Morris et al., 2000), to characterize dehydration behavior of different materials (Rasanen et al., 2003), and to optimize a model formulation for fluid bed granulation (Rantanen et al., 2001). However, NIR sensitivity to water absorbance can also be a disadvantage if the O–H band interferes with other bands of interest.

Raman spectroscopy offers similar advantages to NIR, which enables it to provide on-line physical chemical information linked to final product quality. Raman and NIR probe the vibrational transitions of molecules, providing complimentary information due to different selection rules. Raman spectroscopy utilizes light scattering where an incident photon beam of a specific wavelength is inelastically scattered by molecules. Most incident radiation is either absorbed or elastically scattered (Rayleigh Scatter). A small amount of radiation is modified due to coupling between the photon and the electron cloud of the molecule. Energy can be lost or gained in this process. A "stokes" shift to longer wavelengths (lower energy) or "anti-stokes" shift to shorter wavelengths (higher energy) is detected experimentally (Pelletier, 1999).

One key attribute that enables implementation of quantitative measurements by Raman spectroscopy is the relationship between signal intensity and the concentration of material present in the sampled region. This aspect has produced applications for mapping the composition of drug products and assaying drug pellets, tablets, and solid mixtures (Dao and Jouan, 1993; Ryder et al., 2000; Clarke et al., 2001). These applications take advantage of the proportional relationship between signal intensity and the amount of material exhibiting the vibrational shift (Pelletier, 1999). This quantitative relationship is a critical measurement attribute for successful implementation as a process/product control technique.

A pharmaceutical application that is well-suited to the advantages of Raman is evaluation of drug hydrate state. Raman has been coupled with thermogravimetric analysis (TGA) and simultaneous thermogravimetry and differential thermal analysis (TG/DTA) to monitor desolvation and recrystallization of materials to characterize hydration states of active pharmaceutical ingredients (Bigelow-Kern et al., 2003; Chang and Huang, 2001; Ghule et al., 2003; de Jager and Prinsloo, 2001). Raman measures the effect of water loss on the crystal lattice by the associated change in vibrational states of the molecule. The principle of this application can be extended for monitoring changes in hydration state during fluid bed drying. Fluid bed drying is often used in pharmaceutical manufacturing to remove bulk water from materials after wet granulation. The drying process can produce unstable granulation containing a drug in a non-equilibrium state of hydration. To avoid formation of unstable granulation, processes that do not require drying are utilized, such as direct compression into tablets, encapsulation, or dry granulation. However, in many cases wet granulation yields a more robust process. If wet granulation is being pursued for a formulation where drug hydration state is critical, careful control of the drying process endpoint is necessary to maintain the optimum drug hydration state necessary for proper final product performance. In pharmaceutical drying processes, the endpoint is often determined using a bulk moisture measurement, such as loss on drying. With this method, drug hydration state is inferred from the bulk measurement. In contrast, Raman provides a direct measurement of drug hydration state, which enables a drying endpoint determination that ensures tablet quality.

The purpose of this work was to study the effect of moisture content associated with the risedronate sodium (RS) crystal lattice on the physical stability of tablets. RS is a mixed hydrate containing both lattice water and channel water. Channel water is not an integral part of the lattice, rather it occupies channels formed by the lattice. It can be removed below the boiling point of water and this process is reversible. The hydrate will equilibrate to a stoichiometric amount of water above 20% relative humidity (RH) (Redman-Furey et al., 2005). These properties are not unique to RS. Many materials exhibit similar solid-state hydration properties. For RS channel hydrate, contraction of the crystal lattice occurs when water is removed and expansion occurs when water is gained. If the RS is compressed into tablets while in a partially dehydrated solid-state form, over time changes in tablet properties will be observed as the RS crystal lattice expands and returns to the equilibrium solid-state form.

In these experiments, RS was wet granulated followed by fluid bed drying to produce final granulation moisture contents between 1 and 7%. This moisture content range was chosen to induce variability in RS hydration state. Final granulation moisture at the end of drying can affect the amount of RS solid-state change measured by Raman. In addition, the final granulation moisture, and thus the RS hydration state, can affect the change in tablet properties over time. The granulation was compressed into tablets and the tablets were placed in environments of 22–25 °C with 60 and 75% relative humidity. During drying, the RS solid-state form was continuously monitored by Raman spectroscopy. Raman was the enabling technology used to understand the effect of drug hydration state on final product physical stability.

2. Experimental

2.1. Materials

The formulation in Table 1 was used for these experiments. It consists of risedronate sodium (Procter & Gamble Pharmaceuticals, Norwich, NY, USA), microcrystalline cellulose PH102 (FMC, Philadelphia, PA, USA), povidone (Plasdone K29–32, International Specialty Products, Wayne, NJ, USA), crospovidone (Polyplasdone XL, International Specialty Products, Wayne, NJ, USA), and magnesium stearate (Peter Greven, Bad Münstereifel, Germany). Components (1–3) in Table 1 were used in the granulation.

Table 1
Drug product formulation

Component	Unit (mg)	Batch (g)	%
1. Risedronate sodium	118.5	500.0	47.42
2. Povidone	5.2	22.0	2.09
3. Microcrystalline cellulose PH102	118.5	500.0	47.42
4. Crospovidone	7.6	32.0	3.03
5. Magnesium stearate	0.1	0.5	0.05
Total	250.0	1054.5	100.0

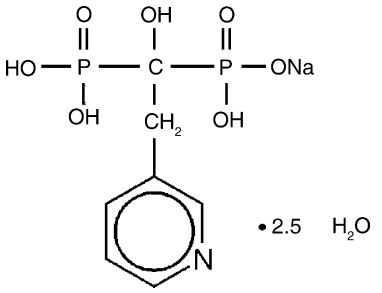

Fig. 1. Risedronate sodium (RS) chemical structure.

Components (4 and 5) were used in the final blend and lubrication blend. The granulating fluid was 204.4 mL of purified water. The formulation in this study is representative of formulations often used in commercial manufacturing, utilizing drug, filler, binder, disintegrant, and lubricant.

The solid-state form of risedronate sodium is hemi-pentahydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na{\cdot}2.5H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium is shown in Fig. 1. The molecular weight of RS hemi-pentahydrate is 350.13. Risedronate sodium is a fine, white to off-white, crystalline powder. It is soluble in water and essentially insoluble in common organic solvents (Physician's Desk Reference, 2003).

A RS level of 47.4% was chosen because it was the minimum amount required to produce suitable signal to noise for quantitation of on-line Raman peaks in the C–H stretching region and the spectral region containing the 3-picoline ring and PO_2^- stretches. The Raman spectra of risedronate at equilibrium are shown in Fig. 2. A detailed spectroscopic characterization of risedronate has been reported by Redman-Furey et al. (2005). Microcrystalline cellulose is a common tablet filler that aids in compression, and its Raman spectrum displays less interference with RS than lactose, another common filler. Lactose produced Raman bands that interfere with the RS Raman bands used to monitor the solid-state form of RS. The Raman spectrum of microcrystalline cellulose is shown in Fig. 3. Povidone is the binder and crospovidone is the disintegrant, and they are routinely used in tablet formulation (*Handbook of Pharmaceutical Excipients*, 2003). For this formulation, 2% povidone and 3% crospovidone were below the limit of detection of Raman spectroscopy. A minimal amount of magnesium stearate was required for lubrication, due to additional lubrication provided by microcrystalline cellulose (*Handbook of Pharmaceutical Excipients*, 2003). Due to the hydrophobic nature of magnesium stearate, the amount in the formulation was minimized to reduce potential interference with the rehydration of RS.

The tablet storage environment temperature and relative humidity were controlled using saturated salt solutions in sealed chambers. Tablets were stored at 22–25 °C under 60 and 75% relative humidity. The 60% RH chamber was made using a saturated solution of sodium dichromate dihydrate (VWR). The 70% RH chamber was made using a saturated solution of sodium chloride (VWR).

2.2. Equipment

The manufacturing equipment used was a N-50 Hobart mixer, a peristaltic pump (Masterflex), a #6 handscreen, a GPCG-1 fluid bed (Glatt Air Techniques), a 10-station Piccola instrumented tablet press (SMI), and modified oval tooling (Natoli).

Instrumentation utilized in these experiments was a moisture balance (Denver), a Raman Holoprobe 785 (Kaiser Optical Systems), a ball probe (Center for Process Analytical Chemistry, University of Washington), a PE360 balance (Mettler), a hardness tester (Schleuniger), and digital calipers (Mitutoyo).

A moisture balance was utilized for testing in-process granulation moisture. Moisture balance parameters were optimized to remove bulk and RS channel water, since RS lattice water is not removed under fluid bed drying conditions. Moisture balance results are directly related to changes in RS solid-state form produced during the drying process. In contrast, Karl Fischer analysis includes RS lattice water producing a bias not related to solid-state changes associated with the removal of channel water.

2.3. Manufacturing process

Risedronate sodium, microcrystalline cellulose, and povidone were combined in the mixer, then purified water was sprayed onto the mixture at a rate of 100 mL/min. The wet mass was hand screened through

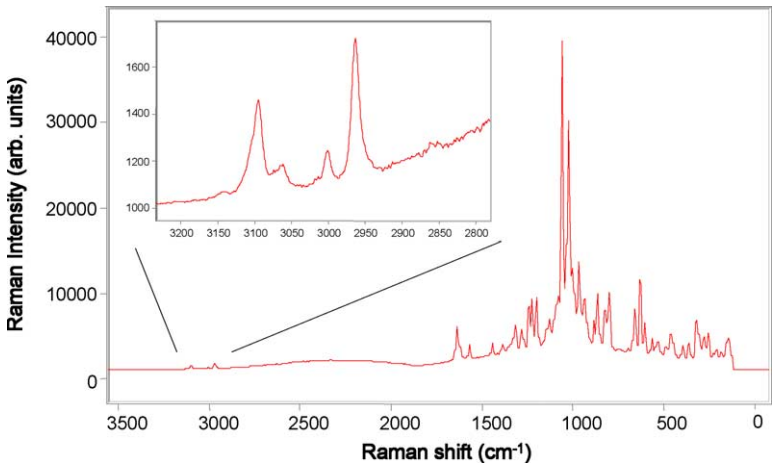

Fig. 2. Risedronate sodium (RS) Raman spectrum at equilibrium.

a #6 screen into the fluid bed. The mass was dried in the fluid bed to moisture contents between 1 and 7%, as determined by a moisture balance. Throughout the drying process, the mass was monitored by Raman spectroscopy. Raman allowed detection of changes in drug hydration state during the drying process. The fiber optic probe head was inserted into the fluid bed through a solution addition port (Fig. 4). This single point probe placement allows for representative sampling during the fluid bed drying process due to the small size of the fluid bed bowl, combined with the high probability that the wet granulation contains homogeneous distribution of RS. The Glatt GPCG-1 is a small fluid bed (bowl height 22 in.) with a high number of turnovers of the material and no significant temperature gradient across the bowl. During the drying process, Raman spectra were collected every 2 min, with a 5 s delay between acquisitions to allow for shaking of the filter bags. The 2 min sampling interval allowed for averaging of about 60 bed turnovers, which is a representative sampling of the entire mass. The estimated sample size is 18 mg per acquisition. A typical thief sample for loss on drying analysis is 1–3 g. In addition, Raman spectra were acquired from material near the location in the fluid bed bowl that was sampled by the thief. The Raman sampling is representative of the total mass when compared to loss on drying. The dried granulation was blended with crospovidone and then

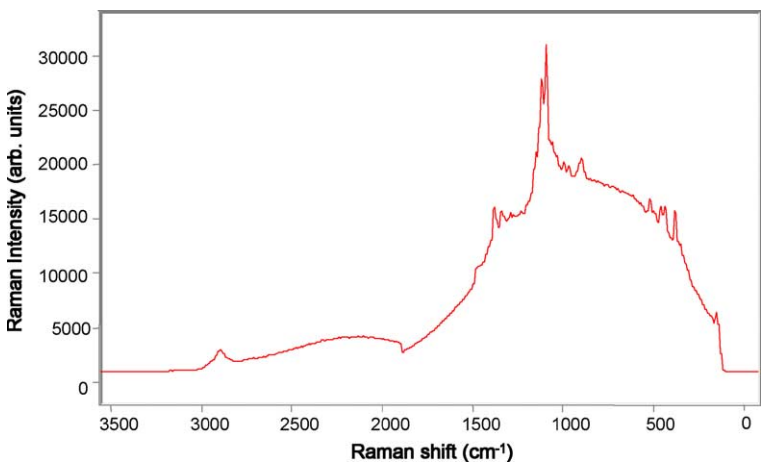

Fig. 3. Microcrystalline cellulose Raman spectrum.

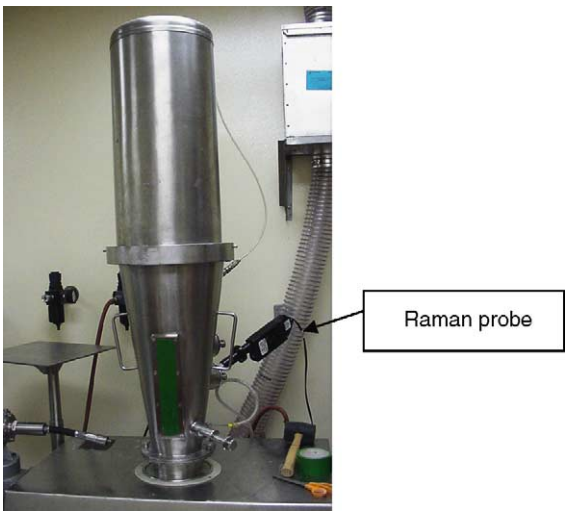

Fig. 4. Fluid bed and Raman set-up.

magnesium stearate in the mixer. The final blend was then compressed into tablets. The number of tablets compressed for each batch was 4220. The manufacturing process is illustrated in Fig. 5.

2.4. Experimental design

The drug hydration state was varied by performing a design of experiments (DOX) on the fluid bed drying process. Fluid bed drying processes are controlled by inlet air humidity, flow rate, and temperature. In this experiment, the inlet air temperature and final granulation moisture content were varied to produce a range of RS hydration states. Although there was no humidity control on the GPCG-1, the inlet air humidity during the experiments was consistent from lot to lot. The inlet air flow was controlled from lot to lot to maintain a consistent state of fluidization in the bed and prevent entrainment of particles into the filter bags. The DOX was a two-factor full factorial with one centerpoint. The DOX is outlined in Table 2.

Table 2
Design of experiments

Experiment number	Inlet air temperature (°C)	Final moisture content (%LOD)
1	30	1
2	30	6
3	60	1
4	60	6
5	45	3.5

During experimentation, the condition of 30 °C inlet air temperature and 1% final granulation moisture content could not be reached within the time scale of the process due to the thermodynamics of the system. The design of experiments was then modified to the conditions illustrated in Table 3. Two additional conditions were added to replace the 30 °C inlet air temperature and 1% final granulation moisture content condition.

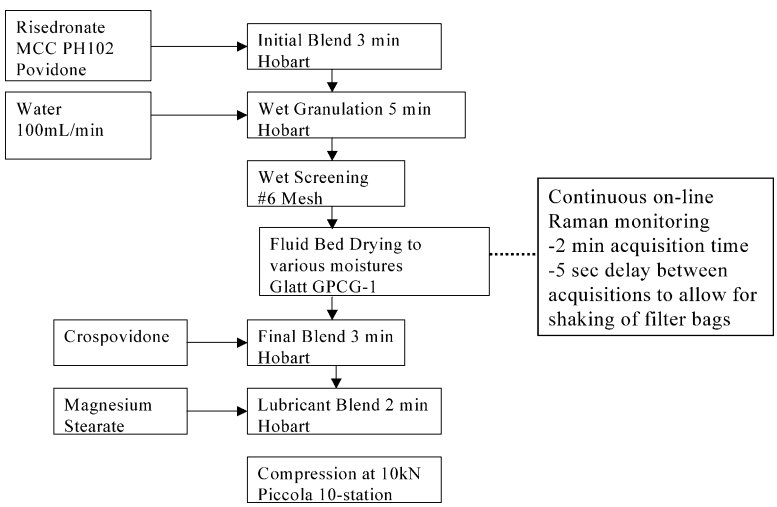

Fig. 5. Manufacturing process flowchart.

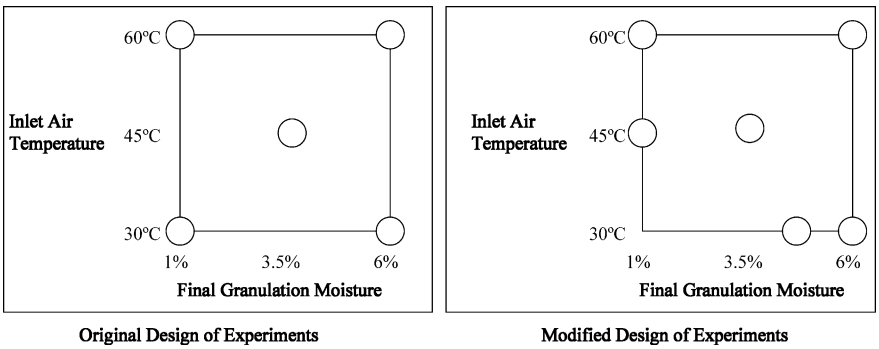

Fig. 6. Fluid bed drying design of experiments.

One condition was 30 °C inlet air temperature and 4.6% final granulation moisture content. The second condition was 45 °C inlet air temperature and 1.5% final granulation moisture content. This modification allowed for an adequate number of experiments for statistical analysis. The original and modified designs of experiments are illustrated in Fig. 6. In addition, a placebo run was performed to produce granulation with a moisture content of 1.4%. Controlling the final moisture content by thief sampling and testing with the moisture balance produced slight differences between actual and target final granulation moisture values. Differences between target and actual moisture content is due to a 5 min delay between taking a sample and receiving the moisture balance result, during which the product is exposed to the drying conditions of the process.

Tablets from each experiment were stored at 22–25 °C, 60 and 75% RH, and tested at 0, 1, 2, 3, 15, 24 h, 1, 2, 3, 6, and 9 months. The tablet properties monitored as a function of time were expected to change if the RS rehydrated during storage. These tablet properties were appearance, weight, thickness, hardness, and moisture content. These properties can impact routine release testing and downstream processing. Tablet appearance is a routine release test in which the severity of the problem, as well as the size of the batch, determines the number of tablets tested and the number of failures allowable. Tablet weight is used in weight variation analysis to demonstrate uniformity of dosage units (US Pharmacopeia XXVII, 2004). If tablet weight increases due to hydration over time, tablet weight variation could exceed the limit of 85.0–115.0%. Tablet thickness is important for further processing such as coating, printing, and packing. Tablet moisture content is important since it affects the tablet mass and thus weight variation results. In addition, it can have an effect on the chemical stability of the tablet; however, the effect on chemical stability was not addressed in this work.

Table 3
Revised design of experiments

Experiment number	Inlet air temperature (°C)	Final moisture content (%LOD)
1	30	5.8
2	60	1.1
3	60	6.6
4	30	4.6
5	45	3.7
6	45	1.5
7[a]	60–75	1.4

[a] Placebo run.

In these experiments, the effect of fluid bed inlet air temperature and final granulation moisture content on the change in RS Raman peak areas from the start to end of the drying process was evaluated using the statistical software package Design-Expert Version 6.0.4, Stat-Ease, Inc. A running median approach ($n = 5$) was used to pre-process the peak areas. In addition, the effect of fluid bed inlet air temperature and final granulation moisture content on the change in tablet properties was analyzed for statistical significance. This analysis utilized the difference between initial results and results after 15 h at 60% RH. The condition of 15 h at 60% RH was used for analysis rather than 24 h at 60% RH, because at 24 h the thickness of tablets manufactured with low moisture granulation (<2% moisture) could not reliably be measured due to substantial tablet

swelling. Similarly, data from tablets stored at 75% RH were not used for statistical analysis, because tablets made from low moisture granulation (<2% moisture) swelled to the point of breaking after only 3 h.

3. Results and discussion

3.1. Raman changes during fluid bed drying

Previous studies showed that Raman spectroscopy was capable of monitoring RS solid-state changes due to dehydration (Bigalow-Kern et al., 2005). Results from these experiments demonstrated feasibility of Raman for monitoring RS solid-state changes during fluid bed drying. In these experiments, Raman was used to relate risedronate solid-state changes during fluid bed drying to the physical stability of tablets. The applicability of Raman to these measurements is limited to materials, which display a detectable change in their Raman spectrum due to crystal lattice changes upon dehydration. Raman spectra from the start of fluid bed drying and the end of drying to 1.1% moisture are shown in Fig. 7. These spectra illustrate the changes that occur during risedronate granulation dehydration in a fluid bed. Fig. 8 shows specific spectral changes in the C–H stretching region and the region containing the 3-picoline ring and PO_2^- stretches corresponding to changes in RS hydration state observed under static laboratory conditions. The largest spectral changes were observed in the C–H stretching region. As peak area decreased at a Raman shift of 2963 cm^{-1}, a new peak formed at 2936 cm^{-1}. Significant changes also occurred in the region including the 3-picoline ring and PO_2^- stretches, as peak area decreased at a Raman shift of 1000 cm^{-1}. Definitive assignment of this band is difficult due to the overlap of bands associated with the 3-picoline ring deformation and PO_2^- stretches. Additionally, assignment of this band is difficult because it is a minor band in both IR and Raman and the fluorescence of microcrystalline cellulose interferes with these spectral features. Changes in this region during dehydration were expected based on hydrogen bonding with channel water. However, changes in the C–H stretching region were not expected since typically C–H functional groups are not associated with hydrogen bonding. For change to occur in the C–H stretching region, the loss of channel water must be significantly disturbing the crystal lattice.

The Raman spectral changes that occurred during fluid bed drying at Raman shifts of 2963, 2936, and 1000 cm^{-1} are shown in Fig. 9. These spectral changes were consistent with the laboratory feasibility experiments shown in Fig. 8. Raman spectra collected on-line during fluid bed drying displayed poorer signal to noise as compared to spectra collected under static laboratory conditions. On-line measurements produced spectra at the threshold of measurement capability, displaying

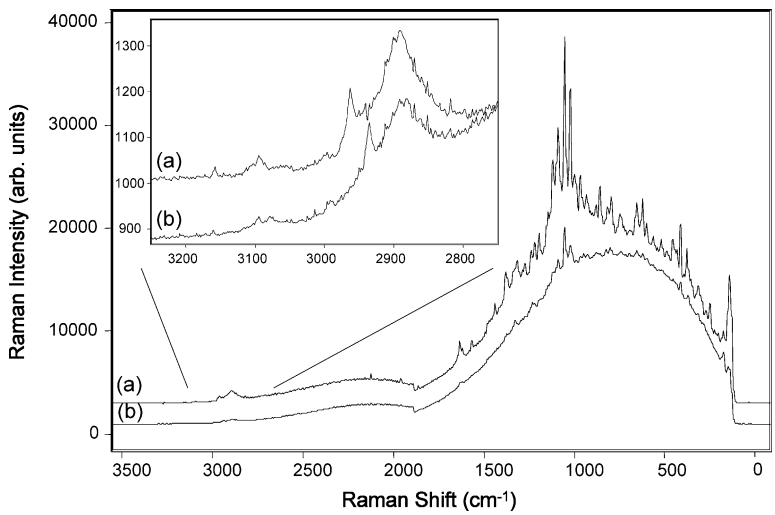

Fig. 7. On-line Raman granulation spectrum: (a) start of drying and (b) end of drying to 1% moisture.

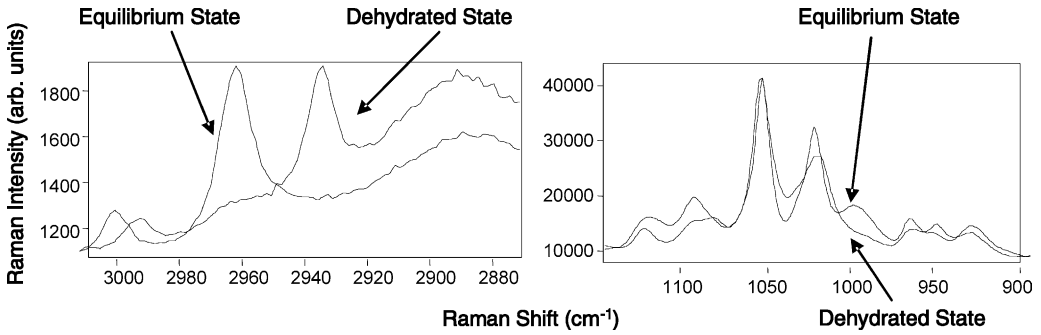

Fig. 8. Raman spectral changes during dehydration at laboratory scale.

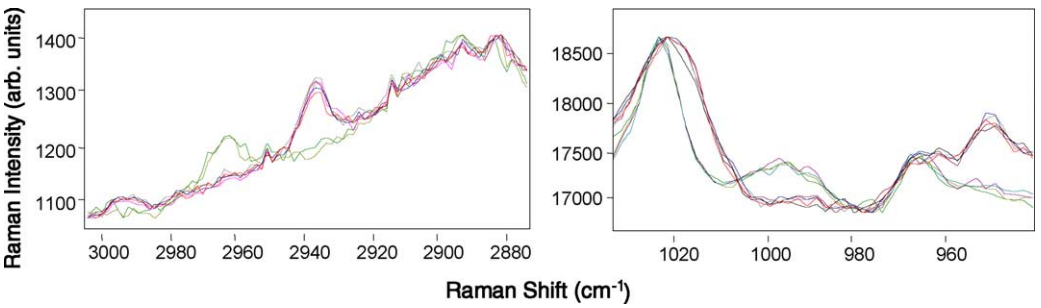

Fig. 9. Raman spectral changes during fluid bed drying.

a signal to noise ratio of approximately 3 in these stretching regions. A number of factors affect Raman signal including probe design, analyte concentration (i.e. number of particles per unit volume), and Raman scattering cross-section of the analyte. The movement of material in the fluid bed caused slight differences in local RS concentration. This variation in particle concentration is reflected in Raman signal intensity. In addition, RS has a modest Raman scattering cross-section, which is approximately an order of magnitude less than naphthalene. To overcome limitations caused by modest scattering cross-section of RS, the amount of RS in the formulation was set at slightly above that needed to achieve measurement capability. The resulting percent RS in the formulation is within the limits of routine formulation development.

The effect of inlet air temperature and final granulation moisture on the solid-state form of RS was analyzed using the change in peak area at Raman shifts of 2963, 2936, and 1000 cm^{-1}. These peaks were chosen for analysis because their change in peak area correlated best with the change in tablet properties. Peaks at 2963 and 1000 cm^{-1} are associated with the equilibrium RS hemi-pentahydrate and 2936 cm^{-1} is associated with dehydrated RS. The results showed that final granulation moisture had a significant effect on the solid-state form. Inlet air temperature had a moderate effect on the change at 2963 cm^{-1} and no effect on changes at 2936 and 1000 cm^{-1}. The significance of inlet air temperature and final granulation moisture on the change in Raman peak areas is shown in Table 4. The effect of final granulation moisture content on the change in RS hydration state measured by the change in Raman peak areas at 2963 and 1000 cm^{-1} is shown

Table 4
Significance of inlet air temperature and final granulation moisture on the change in Raman peak areas

Response: Change in Peak Area	2963 cm^{-1}	2936 cm^{-1}	1000 cm^{-1}
Source	Prob > F	Prob > F	Prob > F
Inlet Air Temperature	0.0907	0.3308	0.4952
Final Granulation Moisture	0.0080	0.0490	0.0050
		statistically significant	
		moderately significant	
		not significant	

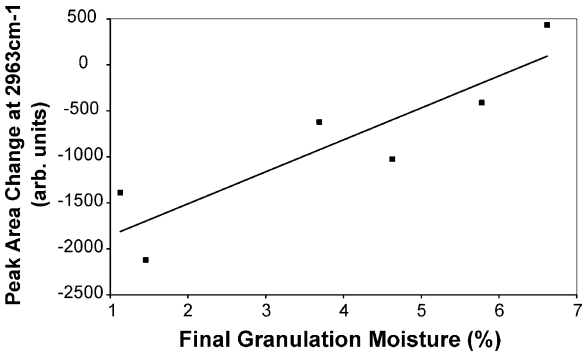

Fig. 10. Effect of final granulation moisture on the change in RS hydration state (Raman shift of 2963 cm^{-1}).

in Figs. 10 and 11, respectively. The correlation coefficients from regression of the change in Raman peak areas at 2963 and 1000 cm^{-1} and the final granulation moisture after drying were 0.79 and 0.94, respectively. The root mean square error was 364 for 2963 cm^{-1} and 2822 for 1000 cm^{-1}. These figures show a strong correlation between the final moisture content of the dried granulation and the hydration state of RS. The dehydration profiles of RS measured by Raman at 2963 and 1000 cm^{-1} during fluid bed drying are shown in Figs. 12 and 13, respectively. The results were normalized for these profiles, to better illustrate the effect of drug hydration state on the change in peak area.

Substantial changes in RS Raman spectral bands were observed when the final granulation was dried to <5.8% moisture, indicative of substantial changes in the RS solid-state structure. The theoretical moisture content of RS at equilibrium is 12.9%. RS contains one

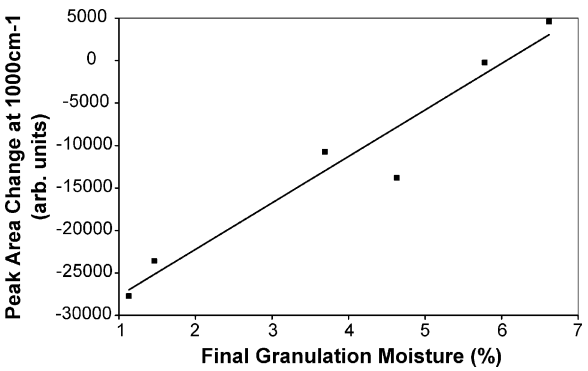

Fig. 11. Effect of final granulation moisture on the change in RS hydration state (Raman shift of 1000 cm^{-1}).

mole of lattice water, which accounts for 5.14% moisture, and one and a half moles of channel water, which accounts for 7.71% moisture. Only channel water is lost during the fluid bed drying process. In addition, the microcrystalline cellulose can lose water during fluid bed drying. The moisture content of the microcrystalline cellulose was 4.35%. Assuming RS and microcrystalline cellulose dehydrate at similar rates, blends dried to less than 6% moisture should produce detectable changes in RS hydration state for this formulation.

3.2. Tablet property changes

Directly after the RS granulation was dried, it was final blended and compressed into tablets. Tablet appearance, weight, thickness, and hardness were measured over time for tablets in 60 and 75% RH chambers at 22–25 °C. The condition of 22–25 °C and 60% RH was used because 25 °C and 60% RH is the long-term stability condition in the ICH stability guideline entitled Stability Testing of New Drug Substances and Products Q1A(R2) (ICH Steering Committee, 2003). An accelerated condition of 22–25 °C and 75% RH was also used. The initial properties of the tablets from each batch are shown in Table 5. Tablets made with granulation at less than 5.8% moisture fractured in a 24 h period at 60 and 75% RH, due to RS rehydration. Placebo tablets made with granulation at 1.4% moisture remained integral under the same conditions, confirming that the RS rehydration was causing the tablets to lose integrity.

Final granulation moisture has a significant effect on RS hydrate state. Therefore, to understand the effect of RS hydrate state on the change in tablet properties, a statistical analysis to determine the effect of final granulation moisture on the change in tablet properties was performed. Also, the effect of inlet air temperature on the change in tablet properties was determined, but was expected to have little to no effect since it had little effect on RS hydrate state. The change in tablet properties used for statistical analysis was the difference between the initial tablet property and 15 h at 60% RH. The statistical analysis showed that the final granulation moisture, thus the RS hydrate state, had a significant effect on the increase in tablet thickness and increase in tablet moisture due to RS rehydration. Final granulation moisture had a moderate effect on

Table 5
Initial tablet properties

Experiment number	Inlet air temperature (°C)	Final moisture content (%LOD)	Average weight (g)	Average thickness (mm)	Average hardness (kp)
1	30	5.8	0.2487	3.87	11.8
2	60	1.1	0.2510	4.02	12.3
3	60	6.6	0.2459	3.79	12.9
4	30	4.6	0.2527	3.99	12.2
5	45	3.7	0.2501	3.98	11.5
6	45	1.5	0.2484	3.96	10.6
7[a]	60–75	1.4	0.2516	4.43	30.4

[a] Placebo run.

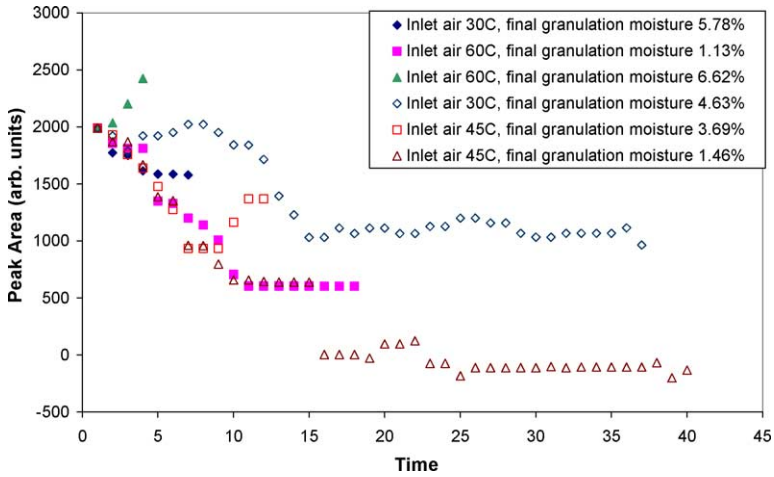

Fig. 12. RS dehydration profile at a Raman shift of 2963 cm^{-1}.

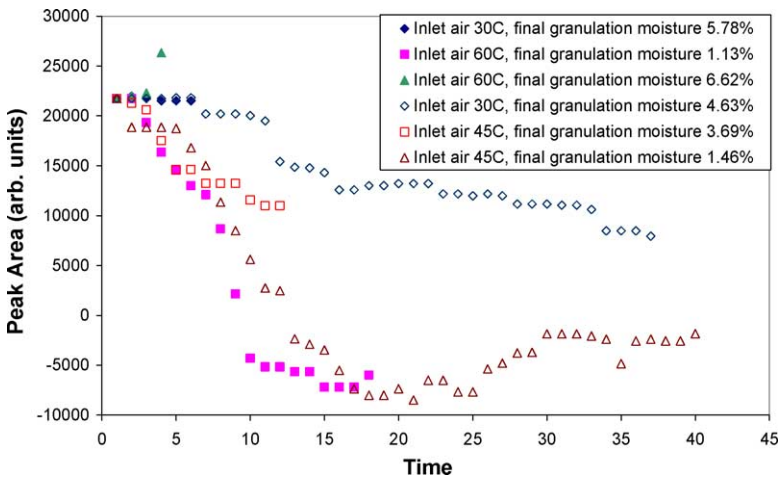

Fig. 13. RS dehydration profile at a Raman shift of 1000 cm^{-1}.

Table 6
Significance of inlet air temperature and final granulation moisture on the change in tablet properties

Response: Change in Tablet Properties	Weight	Thickness	Moisture	Hardness
Source	Prob > F	Prob > F	Prob > F	Prob > F
Inlet Air Temperature	0.0502	0.9541	0.1601	0.6264
Final Granulation Moisture	0.1105	0.0015	0.0287	0.0990
Inlet Air Temp×Final Gran. Moisture	0.0033			
		statistically significant		
		moderately significant		
		not significant		

the decrease in tablet hardness. The increase in tablet weight was significantly affected by the interaction of inlet air temperature and final granulation moisture. The significance of inlet air temperature and final granulation moisture on the change in tablet properties is shown in Table 6. As the RS rehydrated, the moisture in the tablet increased which caused an increase in tablet weight. Also, tablet thickness increased as the RS rehydrated and caused expansion of the tablet. This increase in tablet thickness decreased the tablet hardness.

Tablet thickness was most indicative of changes in the RS solid-state form. Tablets made with granulation at a moisture of 5.8% or greater showed little increase in thickness over 24 h at 60% RH. In contrast, tablets made with granulation at moistures less than 5.8% showed significant increases in tablet thickness. After 15 h at 60% RH, tablets made with granulation at moistures less than 1.5% swelled due to expansion of the RS crystal lattice as it rehydrated. These tablets lost structural integrity and their thickness could not be measured. The results are shown in Fig. 14. A similar trend was observed for tablets at 75% RH. However, tablets made with granulation at moistures less than 1.5% lost structural integrity after only 3 h of exposure to this condition. These results are shown in Fig. 15.

Tablets from each lot were held for 9 months at 22–25 °C, 60 and 75% RH. Tablets were tested at 1, 2, 3, 6, and 9 months. The tablet moisture equilibrated across the lots by 1 month to a level of 6–7.5% at 60% RH and 7.5–9% at 75% RH. The rate of equilibration due to water absorption depends on the intrinsic properties of

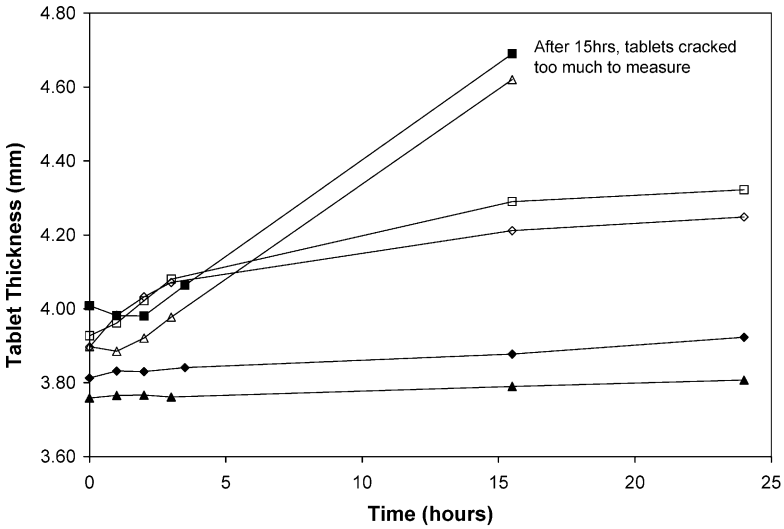

Fig. 14. Effect of RS hydration state on tablet thickness at 22 °C, 60% RH—(♦) inlet air temperature: 30 °C, final granulation moisture: 5.78%; (▲) inlet air temperature: 60 °C, final granulation moisture: 6.62%; (□) inlet air temperature: 45 °C, final granulation moisture: 3.69%; (■) inlet air temperature: 60 °C, final granulation moisture: 1.13%; (◊) inlet air temperature: 30 °C, final granulation moisture: 4.63%; (△) inlet air temperature: 45 °C, final granulation moisture: 1.46%.

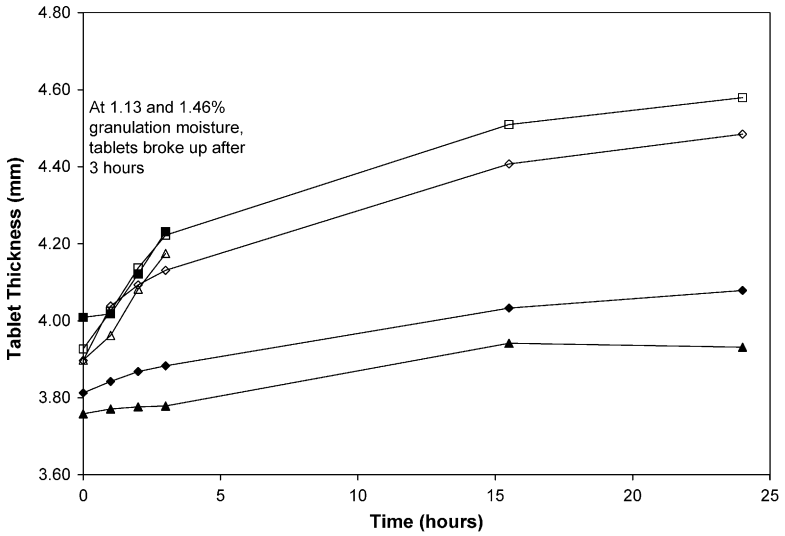

Fig. 15. Effect of RS hydration state on tablet thickness at 22 °C, 75% RH—(♦) inlet air temperature: 30 °C, final granulation moisture: 5.78%; (▲) inlet air temperature: 60 °C, final granulation moisture: 6.62%; (□) inlet air temperature: 45 °C, final granulation moisture: 3.69%; (■) inlet air temperature: 60 °C, final granulation moisture: 1.13%; (◊) inlet air temperature: 30 °C, final granulation moisture: 4.63%; (△) inlet air temperature: 45 °C, final granulation moisture: 1.46%.

the raw materials and the water permeability of tablets. Tablets made with granulation at moisture levels of 5.8% and above maintained a high degree of structural integrity for up to 9 months at 60% RH. However, the structural integrity of tablets made with granulation at moisture levels less than 5.8% was severely compromised within 1 month. Tablet thickness equilibrated by 1 month at 60 and 75% RH. Fig. 16 shows the effect of final granulation moisture, and thus RS hydration state, on tablet thickness at 60% RH over a 9 months period.

3.3. Comparison of Raman results to tablet thickness

Raman is a technique that can probe the structural functionality of a sample. Raman probes the impact of water on the crystal lattice structure of the molecule, without measuring water directly. Removal and addition of water affects hydrogen bonding within the crystal structure and impacts the fundamental vibrational frequencies. For RS, loss of channel water during drying resulted in compression of its crystal lattice. This change was observed by Raman spectroscopy as a peak shift in the C–H stretching region and loss of a peak in the region containing 3-picoline ring deformation and PO_2^- stretches. As RS rehydrated after compression into tablets, expansion of the material occurred as channel water was regained, producing Raman spectra consistent with equilibrated RS hemi-pentahydrate. Rehydration also caused an increase in tablet thickness over time.

These experiments have shown that final granulation moisture has a significant effect on specific Raman spectral changes associated with dehydration of RS and on the change in tablet properties, such as thickness, due to rehydration of RS. A regression analysis was performed to determine if the Raman changes correlated with the observed tablet thickness changes. The results showed that changes in Raman peak areas in the C–H stretching region (shifts of 2963 and 2936 cm^{-1}) and the region containing 3-picoline ring deformation and PO_2^- stretches (1000 cm^{-1}) correlated with the

Table 7
Correlations between change in tablet thickness and change in specific RS Raman peak areas during fluid bed drying

Raman shift (cm^{-1})	Adjusted *R*-squared	*P*-value
2963	0.79	0.0110
2936	0.61	0.0409
1000	0.93	0.0011

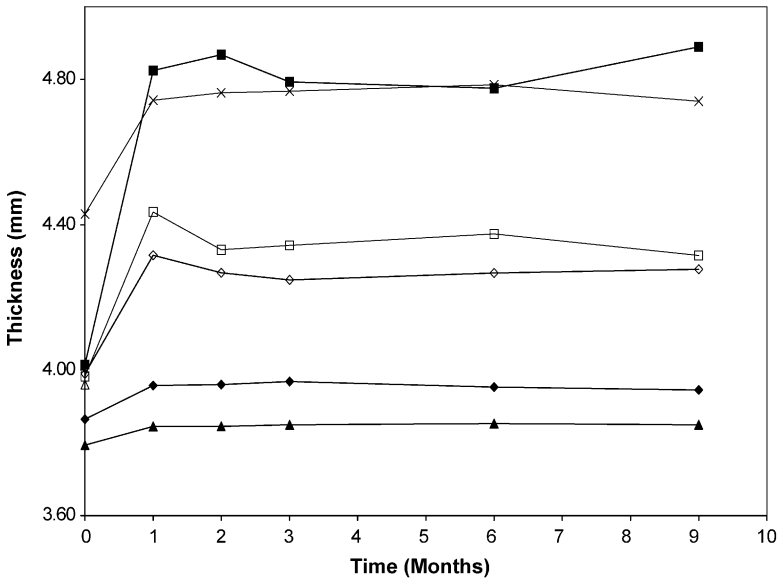

Fig. 16. Effect of RS hydration state on tablet thickness at 22 °C, 60% RH—(♦) inlet air temperature: 30 °C, final granulation moisture: 5.78%; (▲) inlet air temperature: 60 °C, final granulation moisture: 6.62%; (□) inlet air temperature: 45 °C, final granulation moisture: 3.69%; (■) inlet air temperature: 60 °C, final granulation moisture: 1.13%; (◊) inlet air temperature: 30 °C, final granulation moisture: 4.63%; (△) inlet air temperature: 45 °C, final granulation moisture: 1.46%; (×) MCC placebo, final granulation moisture: 1.36%.

change in tablet thickness at 60% RH after 15 h. These results are shown in Table 7.

4. Conclusions

This study demonstrated feasibility for using Raman spectroscopy as an on-line method to monitor drug hydration state during fluid bed drying. On-line Raman spectra collected in these experiments provided critical information that enabled understanding the relationship between risedronate hydration state and the physical stability of tablets. This study also identified a critical process variable, final granulation moisture, for fluid bed drying of risedronate sodium. This variable was critical due to its affect on the solid-state form of risedronate, as measured by Raman spectroscopy, which in turn impacted the physical stability of the drug product over time.

Experimental variables not characterized in these experiments include: alternate drug substances with similar hydration properties, drug and excipients with different Raman scattering cross-sections, the drug concentration, the sensitivity and signal to noise characteristics of the Raman instrument, and the batch size. Batch size will affect the particle concentration the Raman laser probes during fluidization, and thus the signal intensity detected. Under certain conditions, these variables may impact the ability of on-line Raman spectroscopy to monitor solid-state changes during fluid bed drying. To develop this technology as a process control tool, extended characterization of process variables in the context of analytical informing power would need to be completed. More rigorous analysis of the spectral features associated with the change in drug hydration state, and a thorough understanding of critical measurement parameters and their edges of failure is needed.

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